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Analysis of high-throughput sequencing data reveals new genes linked to chronic lymphocytic leukemia

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Johannes Reiter, former PhD student in the group of Krishnendu Chatterjee at the Institute of Science and Technology Austria (IST Austria), is co-author of a *Nature* paper on genetic alterations that drive the progression and relapse of cancer. An international team of scientists from the US, Germany and Austria identified novel genes associated with chronic lymphocytic leukemia through the analysis of high-throughput sequencing data.

Knowing the genetic alterations that provide a selective advantage to the cancer cells is essential for understanding the evolution of cancer and provides the foundation for new therapies. The team of scientists analyzed sequencing data of all protein-coding genes in a genome (called whole-exome sequencing) from 538 chronic lymphocytic leukemia (CLL) patients. CLL is the most common type of leukemia and occurs mostly in adults.

Utilizing sophisticated data analysis methods, the scientists identified 44 genes that are frequently mutated in CLL patients. These mutations are so-called "driver mutations": while cancer cells (as well as normal cells) accumulate many mutations as they age, the driver mutations are those that actually cause the cancer to arise or grow;, while passenger mutations have no functional consequences for cancer growth. 18 of these 44 driver mutations have previously been identified, while the remaining 26 are additional putative CLL driver genes potentially affecting cancer progression. Moreover, the researchers found 11 somatic copy number variations that were present more often than expected by chance. The identified driver genes affect RNA processing and export, the activity of MYC, a transcription factor that plays a role in apoptosis, and MAPK signaling, a signaling pathway implicated in many forms of cancer.

In addition, the authors uncovered genetic features that contribute to a relapse of the disease. The large number of analyzed samples also enabled them to infer which driver mutations arise early and which arise late. They could so study the typical temporal sequence of cancer progression and explore evolutionary relationships among driver genes. Mutations that affect the clinical outcome of the disease were also identified. In particular TP53, SF3B1 and RPS15 mutations were associated with shorter progression-free survival of patients.

This study shows that large sequencing data sets enable the discovery of novel genes associated with cancer as well as the impact of driver gene mutations on relapse and clinical outcome.

Source:
Institute of Science and Technology Austria
